Sphingolipid signaling and hematopoietic malignancies: to the rheostat and beyond.

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Public Summary:
Sphingosine-1-phosphate (S1P) is a bioactive lipid with diverse functions including the promotion of cell survival, proliferation and migration, as well as the regulation of blood vessel formation, inflammation, immunity, vascular permeability and nuclear mechanisms that control gene transcription. S1P is derived from metabolism of ceramide, which itself has diverse and generally growth-inhibitory effects. Regulation of ceramide, S1P and the biochemical steps that modulate the balance and interconversion of these two lipids are major determinants of cell fate, a concept referred to as the "sphingolipid rheostat." There is abundant evidence that the sphingolipid rheostat plays a role in the origination, progression and drug resistance patterns of blood cell-based malignancies. The pathway has also been exploited to circumvent the problem of chemotherapy resistance in leukemia and lymphoma. Here, we summarize recent insights regarding the sphingolipid metabolic pathway and its role in hematopoietic malignancies.

Scientific Abstract:
Sphingosine-1-phosphate (S1P) is a bioactive lipid with diverse functions including the promotion of cell survival, proliferation and migration, as well as the regulation of angiogenesis, inflammation, immunity, vascular permeability and nuclear mechanisms that control gene transcription. S1P is derived from metabolism of ceramide, which itself has diverse and generally growth-inhibitory effects through its impact on downstream targets involved in regulation of apoptosis, senescence and cell cycle progression. Regulation of ceramide, S1P and the biochemical steps that modulate the balance and interconversion of these two lipids are major determinants of cell fate, a concept referred to as the "sphingolipid rheostat." There is abundant evidence that the sphingolipid rheostat plays a role in the origination, progression and drug resistance patterns of hematopoietic malignancies. The pathway has also been exploited to circumvent the problem of chemotherapy resistance in leukemia and lymphoma. Given the broad effects of sphingolipids, targeting multiple steps in the metabolic pathway may provide possible therapeutic avenues. However, new observations have revealed that sphingolipid signaling effects are more complex than previously recognized, requiring a revision of the sphingolipid rheostat model. Here, we summarize recent insights regarding the sphingolipid metabolic pathway and its role in hematopoietic malignancies.